REMARKS/ARGUMENTS

The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

Prior to the present amendment, Claims 28-35, 38-40 were pending in this application. With this amendment, Claims 28-32 have been amended to recite an "isolated native sequence polypeptide." Support for the term "native sequence" can be found in the specification at, for example, page 301, lines 9-21. A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses "naturally-occurring truncated or secreted forms of the specific PRO polypeptide ... naturally occurring variant forms ... and naturally occurring allelic variants of the polypeptide."

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Claims 28-35 and 38-40 are pending in this application.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph. The remaining rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, are addressed below.

I. Information Disclosure Statement

Applicants respectfully thank the Examiner for considering the supplemental Information Disclosure Statement filed on February 2, 2005.

II. Claim Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Pargraph

Claims 28-35 and 38-40 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (Page 3 of the instant Office Action).

Claims 28-35 and 38-40 remain further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art

clearly would not know how to use the claimed invention." (Page 12 of the instant Office Action).

Applicants respectfully disagree and traverse the rejections.

Applicants submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1759 polypeptide.

Utility – Legal Standard

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

In *Cross v. Iizuka*[6] the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11], [12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely

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[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1759 polypeptide.

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[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

The Examiner asserts that "the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon). However, there is no evidence regarding whether or not PRO1759 mRNA or polypeptide levels are also increased in these cancers". The Examiner further asserts that "what is often seen is a lack of correlation between DNA amplification and increased peptide levels." (Page 4 of the instant Office Action).

In support of these assertions, the Examiner refers to the paper by Pennica *et al.* The Examiner further cites Haynes *et al.* as allegedly providing evidence that "polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold." The Examiner also cites Chen *et al.* and Hu *et al.*in support of the assertion that protein expression levels are not strongly correlated with mRNA levels. (Pages 4-5 of the instant Office Action).

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish a necessary correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is imperative to find evidence that protein levels can be "accurately predicted." As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, but whether it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants respectfully submit that, for the reasons previously set forth in the Applicants' response filed on February 2, 2005, Pennica *et al.* does not show a lack of correlation between gene (DNA) amplification and elevated mRNA levels.

The Examiner cites Haynes *et al.* as allegedly providing evidence that "polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold." The Examiner also cites Chen *et al.* and Hu *et al.*in support of the assertion that protein expression levels are not strongly correlated with mRNA levels.

As discussed above, the law does not require the existence of a "strong" or "linear"

correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. According to the authors themselves, the Haynes data confirm that there is a "general trend" between protein expression and transcript levels (page 1863, col. 1), which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. For example, in Figure 1, there is a positive correlation between mRNA and protein levels amongst most of the 80 yeast proteins studied. In fact, very few data points deviated or scattered away from the expected normal and no data points showed a negative correlation between mRNA and protein levels (i.e. an increase in mRNA resulted in a decrease in protein levels). The analysis by Haynes *et al.* is not relevant to the current application. Haynes was studying yeast cells and not human cells. Haynes *et al* notes that their analysis focused on the 80 most abundant proteins in the yeast lysate (page 1867). Haynes *et al.* states "since many important regulatory protein are present only at low abundance, these would not be amenable to analysis" (page 1867). Further, Haynes *et al.* compared the protein expression levels of these naturally abundant proteins to mRNA expression levels from published SAGE frequency tables. (page 1863) Accordingly, Haynes *et al.* did not compare mRNA expression levels and protein levels in the same yeast cells. Thus the analysis by Haynes *et al.* is not applicable to the present application.

Nor is the analysis by Chen *et al.* applicable to the present application. The Examiner cites Chen *et al.* to the effect that twenty-eight of the 165 protein spots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression data.

First, Applicants note that proteins selected for study by Chen *et al.* were those detectable by staining of 2D gels. As noted in, for example, Haynes *et al.* there are problems with selecting proteins detectable by 2D gels. "It is apparent that without prior enrichment only a relatively small and highly selected population of long-lived, highly expressed proteins is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently it is the low abundance proteins that execute key regulatory functions" (page 1870, col. 1). Thus Chen *et al.* by selecting proteins detectable by staining of 2D gels are likely to have excluded from their analysis many of the proteins most likely to be significant as cancer markers.

Secondly, Chen *et al.* looked at expression levels across a set of samples including a large

number of tumor samples (76) along with a much smaller number of normal samples (9). The tumor samples were taken from stage 1 and stage III lung adenocarcinomas, which were classified as bronchoaveolar, bronchial derived or both bronchial and bronchoaveolar derived. Accordingly, the tissues examined were from different tissues in different stages of normal or cancerous growth. The authors determined the relationship between mRNA and protein expression by using the average expression values for all samples. The average value for each protein or mRNA was generated using all 85 lung tissue samples. This resulted in negative normalized protein values in some cases. Further, the authors chose an arbitrary threshold of 0.115 for the correlation to be considered significant. Accordingly, the Chen paper does not account for different expression in different tissues or different stages of cancer.

Thirdly, no attempt was made to compare expression levels in normal versus tumor samples, and in fact the authors concede that they had too few normal samples for meaningful analysis (page 310, col. 2). As a result, the analysis in the Chen paper shows only that a number of randomly selected proteins have varying degrees of correlation between mRNA and protein expression levels within a set of different lung adenocarcinoma samples. The Chen paper does not address the issue of whether increased mRNA levels in the tumor samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumorous versus normal tissue. Accordingly, the results presented in the Chen paper are not applicable to the application at issue.

The correct test of utility is whether the utility is "more likely than not". In the case of the Chen reference, even if the analysis presented is correct (which is disputed), a review of the correlation coefficient data presented in the Chen *et al.* paper indicates that it is more likely than not that increased mRNA expression correlates with increased protein expression. A review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not". Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore,

12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. No genes showed a significant negative correlation. It is not surprising that not all isoforms are positively correlated with mRNA expression. Certain isoforms are likely non-functional proteins. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

The same authors in Chen *et al.*, published a later paper, Beer *et al.*, Nature Medicine 8(8) 816-824 (2002) (copy enclosed) which described gene expression of genes in adenocarcinomas and compared that to protein expression. In this paper they report that " these results suggest that the oligonucleotide microarrays provided reliable measures of gene expression". (pg 317). The authors also state "these studies indicate that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma". Clearly the authors of the Chen paper agree that microarrays provide a reliable measure of the expression levels of the gene and can be used to identify genes whose overexpression is associated with tumors.

Similarly, the references submitted by Applicants (the Ornitoft, Hyman, and Pollack references), also analyzed mRNA and protein expression levels for genes known to be amplified in tumor samples. These papers also indicate that it is more likely than not that increased gene expression levels correlate with increased expression of the protein. The Chen reference does not provide sufficient evidence to dispute this finding.

Finally, the Examiner cites Hu *et al.* to the effect that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease.

Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Applicants respectfully submit that Hu *et al.* does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels.

First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based a statistical analysis of the information disclosed in the published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants submit that the reference by Hu *et al.* only studies the statistical analysis of microarray data and not the gene amplification data. Hence, their findings would not be directly applicable to the gene amplification data. In addition, the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

Further, the analysis by Hu *et al.* has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules were overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, l*et al*one the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (emphasis added).

Accordingly, Applicants respectfully submit that the Examiner has not shown that a lack of correlation between microarray data and the biological significance of cancer genes.

The Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Pennica, Haynes, Hu, and Chen papers do not provide sufficient reasons to doubt the statements by Applicants that PRO1759 has utility. As discussed above, the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. According to the authors themselves, the data in the above cited references confirm that there is a general trend between

protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

The Examiner alleges that "the specification's assertions that the PRO1759 polynucleotides encoding the claimed polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial." (Page 6 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

As stated above, in explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement[18] states, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

As discussed above, the PRO1759 nucleic acid was amplified in a significant number of lung and colon tumors and showed a large increase in gene copy number, *i.e.,* at least 2-fold amplification, in these tumors.

In addition, Example 143 clearly discloses that: "Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers." Applicants further submitted the Declaration by Audrey Goddard, Ph.D. which clearly establishes that the TaqMan realtime PCR method described in Example 143 has gained wide

[18] M.P.E.P. §2107 II (B)(1).

recognition for its versatility, sensitivity and accuracy and is in extensive use for the study of gene amplification. As stated above, Dr. Goddard in her Declaration confirms that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) is significant and useful. The Goddard Declaration further confirms that based on the gene amplification results set forth in Table 8, one of ordinary skill would find it credible that a 2-fold increase in gene copy number (as seen with PRO1759) would indicate that the gene is a diagnostic marker of human lung or colon cancer.

Applicants also submitted the Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and a Director of the Molecular Oncology Department at Genentech, Inc., the assignee of the present application. In his Declaration, Dr. Ashkenazi states, "If gene amplification results in over-expression of the mRNA and corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach."

Accordingly, Applicants respectfully submit that Applicants' assertion that the asserted utility for the PRO1759 polypeptide and its antibodies, for example in the detection of lung or colon cancer, is substantial.

The Examiner contends that the declarations of Dr. Goddard, Dr. Ashkenazi and Dr. Polakis filed under 37 CFR 1.132 (02 February 2005), are insufficient to overcome the rejection of claims 28-35 and 38-40, based upon 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. (Page 6 of the instant Office Action). The Examiner further asserts that "all that the specification does is present evidence that the DNA encoding PRO1759 is amplified in a variety of samples and invites the artisan to determine the significance of this increase." (See page 7 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

First of all, Applicants have previously submitted references by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* As previously stated in the Applicants' response filed on February 2, 2005, these articles collectively teach that in general, gene amplification increases mRNA expression.

Applicants have submitted Dr. Goddard's Declaration to show that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Goddard Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1759 is a diagnostic marker of lung and colon cancer.

The Examiner asserts that "[t]he PRO1759 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1759 nucleic acid was amplified in two cancer samples, to a minor degree (about 2.5 fold). The Examiner further asserts that "Applicant's arguments do not provide data such that the examiner can independently draw conclusions. Only Dr. Goddard's conclusions are provided in the declaration" (Page 7 of the instant Office Action).

Applicants first note that the PRO1759 nucleic acid was amplified in <u>three</u> cancer samples, as shown in Table 8. Applicants next emphasize that the opinions expressed in the Goddard Declaration are all based on factual findings. Thus, Dr. Goddard explains that the TaqMan PCR assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. Further, Dr. Goddard explains that the assay is extremely sensitive technique which leads to accurate determination of gene copy number. Dr. Goddard adds that the TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. For support, Dr. Goddard cites a number of references including a publication by Pennica *et al.* in which Dr. Goddard is a co-author of the paper. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[19] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[20]. Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[21]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[22] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Goddard Declaration) states that "a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy." Therefore, barring evidence to the contrary regarding the above statement in the Goddard Declaration, this rejection is improper under both the case law and the Utility guidelines.

Further, Applicants have submitted Dr. Ashkenazi's Declaration to show that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene product (the protein) is not over expressed. Such experiments are carried out with the HER-2/neu protein in order to select patients for treatment with Herceptin monoclonal antibody therapy, as described in the Hanna paper. Thus the

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[19] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[20] *In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[21] *In re Alton, supra.*

[22] Part IIB, 66 Fed. Reg. 1098 (2001).

PRO1759 polypeptide has utility in conducting such testing, regardless of whether or not the PRO1759 polypeptide is overexpressed.

The Examiner asserts that "Hanna *et al.* supports the instant rejection, in that Hanna *et al.* show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically." (Page 10 of the instant Office Action). Applicants respectfully point out that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (page 1, col. 2)). It is only a subset of tumors which show discordant results. Thus Hanna *et al.* support Applicants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression.

Applicants have clearly shown that the gene encoding the PRO1759 polypeptide is amplified in at least three lung and colon tumors. Therefore, the PRO1759 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1759 gene, that the PRO1759 polypeptide is concomitantly overexpressed.

However, even if gene amplification does not result in overexpression of the gene product (*i.e.*, the protein) an analysis of the expression of the protein is useful in determining the course of treatment, as supported by the Ashkenazi Declaration. The Examiner "agrees that evidence regarding lack of over-expression would be useful" but asserts that "there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not in the instant invention" and that "[f]urther research is required to determine such." (Page 10 of the instant Office Action). The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna paper as experiments involving further characterization of the PRO1759 polypeptide itself. In fact, such testing is for the purpose of characterizing not the PRO1759 polypeptide, but the tumors in which the gene encoding PRO1759 is amplified. The PRO1759 polypeptide is therefore useful in tumor categorization, the results of which become an

important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

Applicants have previously submitted references by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.* As previously stated in the Applicants' response filed on February 2, 2005, these articles collectively teach that in general, gene amplification increases mRNA expression.

The Examiner contends that "Ornoft *et al.* do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time.... Ornoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO1759 in the instant specification. That is, it is not clear whether or not PRO1759 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Ornoft *et al.* is not clear." (Page 11 of the instant Office Action). The Examiner further alleges, "Hyman *et al.* also used CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract).... Therefore, Hyman *et al.* also do not support utility of the polypeptides of the instant invention." (Page 11 of the instant Office Action). The Examiner further alleges that "Pollack *et al*, using CGH technology, concentrate on large chromosome regions showing high amplification (p. 12965). However, Pollack *et al.* did not investigate or show a relationship with amplification and polypeptide expression.... Thus, these references do not teach as Applicants contend that there is a direct correlation between increased mRNA levels and increased levels of encoded protein." (Pages 11-12 of the instant Office Action).

In Ornoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Ornoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Ornoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the

level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Ornoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Ornoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner indicates that Applicants have not indicated whether PRO1759 is in a gene cluster region of a chromosome. (Page 11 of the instant Office Action). Applicants fail to see how this is relevant to the analysis. Ornoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

Applicants respectfully submit that the Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs were hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines were hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and

clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

With regard to the correlation between mRNA expression and protein levels, Applicants previously submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To the date of the Declaration, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels.

Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested according to the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

The Examiner contends that the Dr. Polakis Declaration is insufficient to overcome the rejection of claims 28-35 and 38-40 since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels. The examiner further alleges that the declaration does not provide data such that the examiner can independently draw conclusions. (Page 12 of the instant Office Action).

Applicants submit that Dr. Polakis' Declaration is presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and

the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

As discussed above, the case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[23] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[24] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[25]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[26] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis Declaration, this rejection is improper under both the case law and the Utility guidelines.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and

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[23] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[24] *In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[25] *In re Alton, supra.*

[26] Part IIB, 66 Fed. Reg. 1098 (2001).

the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1759 gene, that the PRO1759 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the claimed PRO1759 polypeptides have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer.

III. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 28-33 and 39-40 additionally remain rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement for the claimed variants and fragments.

Applicants respectfully disagree and traverse the rejection. For the reasons discussed below, Applicants respectfully submit that Claims 28-33 and 39-40 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. [27] [28] Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[29] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[30] [31]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2)

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[27] M.P.E.P. §2164.01.

[28] *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

[29] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (C.C.P.A. 1976).

[30] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (C.C.P.A. 1977).

[31] M.P.E.P. §2164.06.

the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important."[32] [33] "Limitations and examples in the specification do not generally limit what is covered by the claims" M.P.E.P. § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[34]

The specification provides sufficient information to enable the claimed invention

First, Applicants respectfully maintain the position that that Claims 28-33 and 39-40 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response filed on February 2, 2005.

Secondly, Applicant respectfully submit that Claim 33 claims the full-length polypeptide of SEQ ID NO:374, with or without its signal peptide sequence. Applicants have clearly provided the full-length sequence of SEQ ID NO:374 for the PRO1759 polypeptide, and have identified its signal peptide sequence as comprising amino acid residues 1-18 (see, for example, Figure 218). Thus one skilled in the art would easily know how to make the polypeptide, with or with out its signal peptide sequence. In addition, as mentioned above, the polynucleotide encoding PRO1759 was demonstrated to be amplified in lung and colon tumors. Therefore,

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[32] M.P.E..P. §2164.08.

[33] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (C.C.P.A. 1971).

[34] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

based on this information one skilled in the art would have known at the time of filing how to use the full-length PRO1759 polypeptide (SEQ ID NO:374), with or without its signal peptide sequence, in the diagnosis and characterization of lung or colon tumors. Accordingly, Claim 33 (and, as a consequence, those claims dependent from the same) meets the enablement requirement under 35 U.S.C. §112, first paragraph.

Applicants have provided native PRO1759 sequence SEQ ID NO:374. The present application also describes methods for identifying polynucleotides which are amplified in lung or colon tumors. Example 143 of the present application provides detailed protocols and assays for gene amplification in lung and colon tumors. By following the disclosure in the specification, one skilled in the art can easily test whether the gene encoding a variant native sequence PRO1759 polypeptide is amplified in lung or colon tumors. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 302, line 4 to page 305, line 4). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO1759 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making the amino acid sequences (see page 354, line 30 to page 358, line 34) and methods of preparing the PRO polypeptides (see page 358, line 35 and onward).

Therefore, Applicants respectfully submit that one of skill in the art could readily test a variant native sequence polypeptide to determine whether the polynucleotide encoding it is amplified in lung or colon tumors by the methods set forth in Example 143. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:374. Accordingly, one of ordinary skill could practice the claimed invention without undue experimentation.

The Examiner asserts that "Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change ... and the nature and extent of changes that can be made at these positions." (Page 13 of the instant

Office Action). Applicants respectfully point out that the claims are directed to native sequence polypeptides. Thus the nature of the changes to the polypeptide sequence have already been determined by natural evolutionary processes, and need not be tested by the skilled artisan. Further, it is the activity of the encoding polynucleotide, not the polypeptide, that is recited in the claims. Thus considerations of sequences in the polypeptide sequence that are "critical to the protein's structure function relationship" are not relevant.

The claims currently recite polypeptide sequences associated with a biological activity of the encoding polynucleotides. This biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[35]

As discussed above, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that the identification of variant native sequence PRO1759 polypeptides having at least 80% identity to SEQ ID NO:374 wherein the polynucleotide encoding the polypeptide is amplified in lung or colon tumors, can be performed by techniques that were well known in the art at the priority date of this application, and that the performance of such work does not require undue experimentation.

For the above-noted reasons, Applicants respectfully request the Examiner to reconsider and withdraw the enablement rejections under 35 U.S.C. §112, first paragraph.

IV. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-35 and 38-40 are rejected under 35 USC 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to

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[35] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v A.B. Fortia*, 774 F 2d 1104, 227 USPQ 428 (Fed. Cir. 1985)

reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner asserts that Applicants have not "described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO:374, such that it was clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO:374. (Page 16 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection. For the reasons discussed below, Applicants respectfully submit that Claims 28-35 and 38-40 satisfy the written description requirement under 35 U.S.C. §112, first paragraph

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[36] [37] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[38] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [39] [40]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[41] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those

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[36] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[37] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[38] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[39] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[40] *See also* M.P.E..P. §2163 II(A).

[41] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[42] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[43] [44]

The Disclosure Provides Sufficient Written Description for the Claimed Invention

First, Applicants respectfully maintain the position that that Claims 28-35 and 38-40 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response filed on February 2, 2005.

Secondly, Applicants respectfully submit that Claim 33, directed to the full-length polypeptide of SEQ ID NO:374, meets the written description requirement under 35 U.S.C. §112, first paragraph. The Examiner has admitted in the previous Office Action that "an isolated polypeptide consisting of amino acid sequence of SEQ ID NO:374 ... meets the written description provision of 35 U.S.C. §112, first paragraph." (See page 13 of the Office Action mailed on November 4, 2004). Accordingly, claims dependent upon Claim 33 also meet the written description provision of 35 U.S.C. §112, first paragraph.

Next, Applicants have amended Claims 28-32 to recite an isolated native sequence polypeptide. Applicants respectfully submit that the instant specification evidences the actual reduction to practice of a full-length PRO1759 polypeptide of SEQ ID NO:354, with or without its signal sequence. As stated above, the Examiner has acknowledged that a polypeptide comprising the sequence set forth in SEQ ID NO:354 meets the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of native sequence polypeptides with at least 80% sequence identity to SEQ ID NO:354, which possess the functional property of having a nucleic acid which is amplified in lung or colon tumors would meet the requirement of 35 U.S.C.

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[42] *See also* M.P.E.P. §2141.03.

[43] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[44] *See also* M.P.E.P. §2141.03.

§112, first paragraph, as providing adequate written description.

Applicants have provided native PRO sequence SEQ ID NO:354. The present application also describes methods for identifying genes which are amplified in lung or colon cancer.

Example 143 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a native variant PRO1759 protein is amplified in lung and colon tumors. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 302, line 4 to page 305, line 4). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO1759 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specifications sets forth methods for making the amino acid sequences (see page 354, line 30 to page 358, line 34) and methods of preparing the PRO polypeptides (see page 358, line 35 and onward).

Therefore, Applicants respectfully submit that one of skill in the art could readily test a nucleic acid sequence which encodes the variant polypeptide to determine whether it is amplified by the methods set forth in Example 143.

Accordingly, the specification provides adequate written description for native sequence polypeptides having at least 80% identity to SEQ ID NO:354 wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. For the above-noted reasons, Applicants respectfully request the Examiner to reconsider and withdraw the written description rejections under 35 U.S.C. §112, first paragraph.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2830 P1C38**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 21, 2005

By: _____
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